REMARKS

Claim 1 is pending in the present application and is rejected. Applicants are herein amending claim 1.

Claim Amendments

Applicants are herein amending claim 1, without prejudice or disclaimer, to replace "eating disorders" with "anorexia nervosa" and "bulimia nervosa", to delete cocaine addiction, and to replace "sexual dysfunction with "premature ejaculation." Applicants reserve the right to pursue the cancelled subject matter in one or more continuation applications. Applicants submit that the amendment is fully supported by the specification and that no new matter has been added. Support for "anorexia nervosa" and "bulimia nervosa" may be found in the specification, *inter alia*, on page 13, lines 30-31 and "premature ejaculation" may be found on page 13, line 32.

Obviousness-Type Double Patenting

Claim 1 is rejected under the judicially-created doctrine of obviousness-type double patenting as being allegedly unpatentable over claim 21 of US-B-6,617,327. Applicants filed a Petition for a Certificate of Correction on March 7, 2005 in US-B-6,617,327 to delete subject matter that was to have been deleted by Examiner's amendment in the application prior to issuance. The Certificate of Correction appears to have been posted to PAIR on April 7, 2005. Applicants have confirmed through a telephonic discussion with the Examiner that Applicants' actions with respect to the US-B-6,617,327 have rendered moot the rejection of claim 1 of the present application for obviousness-type double patenting. Accordingly, applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, First Paragraph (Enablement)

Claim 1 is rejected for allegedly failing to comply with the enablement requirement under 35 U.S.C. § 112, first paragraph. Applicants respectfully traverse the rejection.

Applicants gratefully acknowledge the Office 's recognition that claim 1 is allowable to the extent that it provides a method of treatment for obesity, bulimia nervosa, vasomotor flushing, alcohol addiction, and premature ejaculation. Accordingly, with respect to the method for providing therapy for various substance addictions, applicants have specified that the claimed method provides treatment for the condition of alcohol addiction. Applicants have also amended claim 1 to specify that the claimed method is directed to treatment of premature ejaculation, as opposed to the entire genus of disorders associated with the term "sexual dysfunction."

Additionally, applicants have amended claim 1 to specify that the claimed method represents treatment for the eating disorders of bulimia nervosa and anorexia nervosa. The Office Action has expressed the recognition that SSRI drugs are a plausible treatment modality for bulimia nervosa, but contends via citation to *Crown* and *Mitchell* that no pharmacological agents, including SSRIs, have been shown to provide effective treatment for anorexia nervosa. Applicants respectfully disagree with the absolute nature of the Office's contention, since numerous sources have reported that SSRI drugs can indeed provide efficacious therapy for subjects afflicted with that eating disorder. For example, *Boyer* reports that at least three separate studies have provided confirmation of the successful use of SSRIs in patient treatment regimens. *See Boyer WF. Potential indications for the selective serotonin reuptake inhibitors. Int Clin Psychopharmacol. 6 Suppl 5, 5-12 (1992)* (attached). Additional studies have confirmed that treatment with SSRIs can be effective in anorectic patients. *See, e.g., Pallanti S, Quercioli L, Ramacciotti, A. Citalopram in anorexia nervosa. Eat Weight Disord. 2(4), 216-21 (1997)* (attached); *Fassino S, Leombruni P, Daga G, Brustolin A, Migliaretti G, Cavallo F, Rovera G. Efficacy of citalopram in anorexia nervosa: a pilot study. Eur Neuropsychopharmacol. 2002 12(5), 453-9 (2002)* (attached).

Thus, while Crown and Mitchell do provide a different viewpoint, there is ample material available to demonstrate that the use of pharmacological agents with SSRI efficacy, such as those disclosed in the instant application, would represent beneficial therapy for subjects suffering from the eating disorder anorexia nervosa. In view of such material, applicants respectfully submit that the Office Action's rejection of claim 1 to the extent that it claims a method for the treatment of anorexia nervosa is inapposite.

Accordingly, because the remaining subject matter of claim 1 has met with approval by the Office Action, applicants respectfully submit that the whole of claim 1, as amended, is in condition for allowance.

Conclusions

In view of the forgoing amendments and remarks, Applicants believe the sole claim pending in this application to be in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please contact the undersigned at 215-568-3100.

Respectfully submitted,

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Introduction

The development in psychopharmacological treatment has placed serotonin as an important neurotransmitter in various psychiatric disorders. The 5-HT reuptake inhibitors seem to be effective in a range of different syndromes such as melancholia, major depression, atypical depression, dysphoria, recurrent brief depression, panic disorder, obsessive compulsive disorders, kleptomania, dementia, pain and alcoholism.

Due to this wide range of syndromes in which effect is reported, it has been suggested, that 5-HT uptake inhibitors should be named emotional stabilizers rather than antidepressants. It is a question whether serotonin plays a specific role in these syndromes, or the 5-HT uptake inhibitors influence a pathway common for all above mentioned syndromes. Maybe we are not even close to finding the central pathogenic mechanism for psychiatric disorders. By means of the selective substances available today, we have a method which leads us to a better understanding of the biology underlying the syndromes. The important issue is, however, that the selective drugs, i.e. 5-HT uptake inhibitors, are clinically effective and of benefit to the patients.

Citalopram is a 5-HT uptake inhibitor, the most selective marketed today. Citalopram has an excellent pharmacokinetic profile, a half-life of about 36 h and a minimal risk of interaction. Further to this, citalopram has only few, mild and transient side effects and is therefore well accepted generally, and also by groups who are sensitive to adverse effects. Citalopram is proven to be effective in depressive patients and excellent results are reported when treating elderly depressed patients with and without senile dementia. Patients suffering from panic disorder have also been treated with good results and high tolerability.

This publication contains proceedings from a symposium held in Florence, Italy, 11 June 1991 at the 5th World Congress of Biological Psychiatry and two further papers. A review of diagnoses in which 5-HT uptake inhibitors are reported effective is given. Serotonin in panic disorder is dealt with in detail. The difference in pharmacokinetic profile between 5-HT uptake inhibitors is reviewed with emphasis on citalopram. The clinical effect of citalopram in depression is illustrated by means of a meta-analysis, and the effect of citalopram in elderly patients is also presented. A view into the future treatment of depression was given as an introduction to the last part of the programme.

In addition, some recent placebo controlled short-term data for citalopram and preliminary evidence on the citalopram efficacy in relapse prevention is also described.

As chairman of the symposium, I express my sincere thanks to the speakers and authors for their contributions.

Rasmus Fog

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Potential Indications for the Selective Serotonin Reuptake Inhibitors

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The selective serotonin reuptake inhibitors (SSRIs) include fluoxetine, fluvoxamine, citalopram, paroxetine and sertraline. These medications may be effective for a variety of indications. The literature clearly supports their efficacy in some of these conditions in major depression. Data concerning their use in other areas is clearly preliminary but promising. These include reports of treatment of obsessive–compulsive disorder, atypical depression, panic disorder, premenstrual tension, eating disorders, substance use disorders, chronic pain, dementia, and personality disorders with aggressive or impulsive features. The variety of clinical uses for the SSRIs may compel re-examination of traditional diagnostic categories and theories of how antidepressants work.

Introduction

The selective serotonin reuptake inhibitors (SSRIs) are an important new class of medications in clinical psychiatry. The class includes fluoxetine, fluvoxamine, citalopram, paroxetine and sertraline. There is a large body of literature supporting their efficacy in major depression (Boyer and Feighner, 1991). As these compounds come into extensive use reports are emerging of their possible efficacy in a wider range of disorders. This review will briefly note some of these areas. The intent will not be to argue that the SSRIs are effective for all of these indications. The lack of controlled data clearly does not allow such a conclusion. Instead the aim will be to alert the reader to areas that bear watching and to consider the implications of these findings.

Obsessive–compulsive disorder (OCD)

A number of double-blind studies of sertraline and fluvoxamine in obsessive–compulsive disorder have been reported. With the exception of one small study (Jenike *et al.*, 1990*a*) these have shown clinically and statistically significant effects in OCD (Perse *et al.*, 1987; Bick *et al.*, 1989; Goodman, *et al.*, 1989; Chouinard *et al.*, 1990; Jenike *et al.*, 1990*b*). One study found fluvoxamine to be significantly superior to desipramine, a relatively more potent noradrenergic uptake inhibitor (Goodman *et al.*, 1990). Fluoxetine has also been studied in a number of open trials with encouraging results (Fontaine *et al.*, 1985; Turner *et al.*, 1985; Jenike *et al.*, 1989; Levine *et al.*, 1989*a*, *b*; Liebowitz *et al.*, 1990; Riddle *et al.*, 1990).

A number of disorders which share features with OCD may also respond to SSRIs. Fallon and colleagues treated seven patients with excessive religious scrupulosity for at

least 8 weeks with fluoxetine or clomipramine. At the end of the trial 5/7 were much improved. These results suggest that extreme moral or religious concerns may be a form of OCD and may be treatable with serotonin reuptake blockers (Fallon *et al.*, 1990). Benarroche reported an 80% response rate of trichotillomania to fluoxetine. All patients relapsed after medication was withdrawn (Parker, 1982). Viswanathan described a patient who experienced severe, recurrent, intrusive, but ego-syntonic fears that she or someone in her family had cancer. This was successfully relieved in two separate trials of fluoxetine, 20 mg b.i.d., but not by desipramine or buspirone (Viswanathan *et al.*, 1991).

Atypical depression

Atypical depression is an important, if imprecisely defined, clinical concept. Some evidence suggests that monoamine oxidase inhibitors (MAOIs) are superior to tricyclic antidepressants for these patients. However use of the MAOIs is limited by the need for dietary restrictions and concern for drug interactions. Pande *et al.* randomly assigned 27 patients with atypical depression as defined by Quitkin *et al.* to 6 weeks of double-blind treatment with fluoxetine 20–60 mg daily or phenelzine, 45–90 mg daily. The results showed 92% response with fluoxetine and 67% with phenelzine. Phenelzine patients also had significantly more side effects. More patients elected to stay on fluoxetine than phenelzine at the end of the trial (Pande *et al.*, 1991).

Panic disorder

Humble and colleagues treated 20 panic disorder patients with citalopram, up to 60 mg/day, in an 8 week open study. Citalopram appeared effective and well-tolerated (Humble *et al.*, 1989). Similar positive effects were reported in two open trials of fluoxetine (Gorman *et al.*, 1987; Schneier *et al.*, 1990). One controlled study has compared fluvoxamine with maprotiline, a noradrenaline uptake inhibitor, in panic disorder. Fluvoxamine was significantly effective but maprotiline was not (Den-Boer and Westenberg, 1988).

Premenstrual tension (PMS)

Two double-blind placebo-controlled studies have shown fluoxetine to significantly decrease the affective symptoms accompanying PMS (Rickels *et al.*, 1990; Stone *et al.*, 1990). However a study with fluvoxamine failed to show significant differences from placebo (Veeninga *et al.*, 1990). This may have been due to the strong placebo effect in this study or it may suggest that all SSRIs are not equally effective in this condition.

Personality disorders

Markovitz and associates treated 22 patients with borderline or schizotypal personality disorders in an open, 12-week trial of fluoxetine. All had initially sought help for anxiety or depression and 13 met criteria for major depression. There were significant reductions in self-injury and in scores on the Hopkins symptom checklist in patients with either or both diagnoses (Markovitz, *et al.*, 1991). Two open studies of fluoxetine have also reported significant improvement in patients with severe borderline personality disorder (Cornelius *et al.*, 1990; Norden, 1991). There are however no controlled studies.

Substance abuse

Naranjo and colleagues tested citalopram in 39 non-depressed males who were early problem drinkers. Citalopram, 20 mg/day, did not show an effect but 40 mg/day decreased the number of drinks consumed and increased the number of abstinent days (Naranjo *et al.*, 1987). These same investigators found similar results with other serotonin reuptake blockers (Naranjo and Sellers, 1989).

Some evidence suggests that fluoxetine may antagonize the reinforcing properties of cocaine (Richardson and Roberts, 1991). Pollack and Rosenbaum gave fluoxetine to 11 cocaine-abusing heroin addicts in a methadone maintenance program. Of the eight patients who completed the trial, five were successfully treated for cocaine use. They concluded that fluoxetine may be a useful addition in the treatment of cocaine abuse (Pollack and Rosenbaum, 1991).

Eating disorders

Weight loss is a common side effect of the SSRIs. Several studies have suggested that fluoxetine or sertraline may be a useful adjunct in the treatment of obesity in non-depressed patients. Fortunately, the degree of weight loss appears to be proportional to the degree of initial obesity (Levine et al., 1987; Orzack *et al.*, 1990), so that weight loss in normal or underweight individuals is rarely a problem.

Clark and Rosenblatt studied 80 obese diabetic patients. Sertraline (150 mg/day) was associated with significantly more weight loss than placebo (2.9 vs. 0.76 kg) (Clark and Rosenblatt, 1989). Similarly, Feighner and Rosenblatt reported significantly more weight loss with sertraline, 50–200 mg/day, than placebo in 150 non-depressed obese outpatients (Feighner and Rosenblatt, 1989).

Weight loss with fluoxetine is associated with higher doses than usually used for depression, in the range of 40–60 mg/day (Levine, *et al.*, 1989*a*). Ferguson and Feighner found that fluoxetine (average 65 mg/day) produced significantly more weight loss than placebo among 150 non-depressed obese outpatients. Fluoxetine was also associated with a trend for more weight loss than benzphetamine (Ferguson and Feighner, 1987). Marcus and colleagues reported that patients treated with 60 mg/day of fluoxetine in addition to behavior therapy lost more weight than those treated with behavior therapy plus placebo (Marcus *et al.*, 1990).

Maintenance of weight loss is a problem with the SSRIs, as it is with other weight-loss strategies. Darga and co-workers compared diet plus either fluoxetine or placebo in the treatment of 45 non-depressed obese patients. The fluoxetine-treated patients lost significantly more weight, but had a tendency to regain it. At the end of 1 year there were no significant differences between the fluoxetine and placebo groups (Darga *et al.*, 1991).

The SSRIs may have beneficial effects in other eating disorders. Enas and colleagues compared two doses of fluoxetine in 382 outpatient bulimic women. At 60 mg/day fluoxetine was significantly superior to placebo. Fluoxetine 20 mg/day had an intermediate

effect (Enas *et al.*, 1989). This dose-response effect is similar to that noted above for weight loss with fluoxetine.

Weltzin and colleagues reported on 31 patients with chronic anorexia nervosa who were treated with fluoxetine for an average of 11 months. During the study 29 patients (94%) maintained their body weight at or above 85% average body weight for height. Global Response was judged to be good in 10, partial in 17 and poor in 6. Paradoxically, patients who were partial or poor responders were significantly more depressed at baseline than good responders (Weltzin *et al.*, 1991). This suggests that fluoxetine's effect may have been independent of its antidepressant activity. Gwirtsman and associates reported that six patients with chronic anorexia nervosa showed improved mood and weight gain with fluoxetine (Gwirtsman *et al.*, 1990). Ferguson reported successful use of fluoxetine in another patient with anorexia nervosa (Ferguson, 1987).

Other potential indications

Goldman and Janecek gave fluoxetine, 20 mg/day, to eight patients with schizophrenia in an open trial (Goldman and Janecek, 1990). Clinical state improved in all patients. Violent incidents decreased, while participation in programs and socialization increased. The addition of fluoxetine to neuroleptic medication has also been reported to be helpful in other patients with chronic schizophrenia (Goff *et al.*, 1990; Lindenmayer *et al.*, 1990).

Kafka reported that 9/10 men with DSM-III-R non-paraphilic sexual addiction or paraphilias had improved sexual behaviors while treated with fluoxetine, imipramine, or lithium (Kafka, 1991*a*). Kafka also reported that fluoxetine successfully treated a rapist with intrusive and persistent paraphilic rape fantasies. Symptoms of impulsiveness, anxiety and depression were also markedly improved (Kafka, 1991*b*). Another investigator reported the successful use of fluoxetine in treatment of a fetish (Lorefice, 1991).

Todd reported three cases of autism in which fluoxetine, 20 mg/day, was helpful in reducing behaviors such as stereotypies rituals, and violent outbursts (Todd, 1991). Ghaziuddin and colleagues presented four more cases of autism in which fluoxetine was helpful, especially in the presence of concomitant depression (Ghaziuddin *et al.*, 1991).

The SSRIs also improve some of the emotional and behavioral symptoms that accompany dementia (Nyth *et al.*, 1987, 1989; Martin *et al.*, 1989; Sobin *et al.*, 1989). Whether there is any primary improvement in memory function is unsettled.

Hanzel and associates compared fluoxetine with protriptyline in 12 patients with obstructive sleep apnea. Both drugs decreased periods of apnea and hypopneas, but fluoxetine was better tolerated (Hanzel *et al.*, 1991).

Pain is another area in which the SSRIs may be helpful. Theesen and March (1989) reported a patient with painful diabetic neuropathy and major depression, both of which responded to fluoxetine. Fluoxetine may also have some use in the treatment of headache (Diamond and Freitag, 1989) and fibrositis (Geller, 1989).

Discussion

An important theoretical question is how one class of medication could be helpful for such a disparate group of disorders. Part of this dilemma is artifactual: it is relatively common for patients with one disorder, for example borderline personality disorder, to present with features of other disorders. In this case the SSRI may be treating a feature of an associated disorder and contributing only indirectly to improvement in another.

Another hypothesis is one put forward by Van Praag and others; that abnormal serotonin function affects behavior in ways that cross traditional nosologic boundaries. For example, disturbed serotonin function may be related to depressed mood, anxiety, impulsivity, and aggression (Apter *et al.*, 1990). Many of the conditions for which the SSRIs are helpful have varying degrees of these features. The implication of this theory is that traditional nosologic boundaries may need to be re-examined in light of this biochemical and pharmacologic data.

A related possibility is that abnormalities in serotonin function may only begin a pathologic process, the ultimate form of which is shaped by the social environment, intrapsychic factors or other biological conditions. This is an interesting possibility as it is reminiscent of earlier psychodynamic formulations regarding symptom "choice".

Another hypothesis is that SSRIs may have a therapeutic effect which is unrelated to the etiology of the disorder. There are many examples of illnesses in which effective treatments do not act on the cause of the illness. Diuretics are helpful for hypertension although high blood pressure is rarely, if ever, caused by water or salt retention. Insulin is used in type II diabetes even though the pathology lies in sub-sensitivity to insulin rather than lack of insulin. Histamine-1 receptor blockers and antacids are mainstays of therapy for gastrointestinal ulcers although ulcers are not caused by an excess of histamine and only rarely by excessive acid production. These speculations on the apparently broad range of indications for the SSRIs are also of course not mutually exclusive. It will be very interesting to follow these areas to see which alternatives are supported.

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Clinical Pharmacokinetics of Citalopram and Other Selective Serotonergic Reuptake Inhibitors (SSRI)

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The pharmacokinetics and clinical properties of clomipramine, the classic 5-HT uptake inhibiting antidepressant is well known. Within the last years, several new and more selective serotonin uptake inhibitors have been introduced in clinical practice, including trazodone, citalopram, paroxetine, femoxetine, fluvoxamine and fluoxetine. They differ by their chemical structure, and therefore, important differences can be expected with respect to their metabolism and kinetics in man. In this presentation, the following points will be addressed: Present knowledge about their metabolism and their kinetics, taking into account that most of them are racemates, whose clinical role is only partially understood, including that of the metabolites. It will further be examined whether they are candidates for a genetic polymorphism of metabolism of the debrisoquine-spartein-dextromethorphan type. This may e.g. be suspected for fluoxetine which interferes strongly with the metabolism of tricyclic antidepressants. Finally, data of the literature will be analysed about a possible relationship between the clinical efficacy of these drugs and their plasma levels, including those of their active metabolites.

Introduction

The classical tricyclic antidepressants have many similarities in pharmacodynamics and pharmacokinetics, as a consequence of their common chemical structure. Nevertheless, they differ widely in potency and selectivity and inhibition of the reuptake of serotonin and norepinephrine (Table 1). Within the last few years, several more potent and more selective serotonin reuptake inhibitors (SSRI) have been introduced as antidepressants in clinical practice or are still under investigation (Feighner and Boyer, 1991). These include citalopram, femoxetine, fluoxetine, fluvoxamine, paroxetine and sertraline, not to forget the earlier introduced drug trazodone for its selectivity but low potency (Table 1).

The pharmacological profile—chemical structure relationship of SSRIs

Among the tricyclic antidepressant drugs, clomipramine is considered to be the most potent 5-HT reuptake inhibitor *in vitro*. However, due to the presence of its metabolite demethylclomipramine, a potent norepinephrine reuptake inhibitor, the plasma concentrations of which often exceed those of the parent compound, clomipramine loses *in vivo* much of its selectivity. Among the new SSRIs, paroxetine is the most potent, and citalopram the most selective serotonin reuptake inhibitor. Citalopram's main metabolite,

BRIEF REPORT AND NEW HYPOTHESES

Citalopram in anorexia nervosa

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ABSTRACT. *Thirthy-two female patients who had been diagnosed as having anorexia nervosa restricting subtype according to the DSM IV (Diagnostic and Statistical Manual of Mental Disorders-IV), were enrolled in a 6-month open trial with citalopram at a starting dose of 20 mg. At the end of the trial, 46.9% of the patients showed a satisfactory response, 34.4% an unsatisfactory response, improvement criteria being weight improvement, menstruation and score reduction on the Symptoms Checklist 90R. Anorectics also showed significant improvement in several Eating Disorder Inventory-2 (EDI-2) scores at the end of the trial, with greater improvement related to satisfactory response to citalopram. Data suggest that SSRI (Selective Serotonin Reuptake Inhibitor) Citalopram could be effective at least in a subgroup of anorectic patients, both on clinically objective and on subjective aspects of anorexia nervosa.*

(Eating Weight Disord. 2, 216-221, 1997).

INTRODUCTION

The utility of SSRIs in the treatment of eating disorders has been indicated by a number of different studies (1, 2), though not without some controversy, especially as regards anorexia, where there is ongoing debate about the efficacy of SSRIs and their utility and safety in the clinical management of anorectics (3, 4).

Since the first study by Mills (5), which was then repeated in double-blind tests by Biederman (6) and Halmi et al. (7) with amitriptyline, the use of active drugs on the serotonin system has been amongst the most widely-practiced; clomipramine has also been used in double-blind studies (8), with results that have not, however, been significant. For the SSRIs the results of open studies with fluoxetine (9, 10) seem to be encouraging but in the absence of a double-blind placebo-controlled evaluation of SSRI therapy in patients with anorexia nervosa, pharmacological treatment, apart from that for the comorbid conditions, must be recommended under care control.

It is not well-documented whether the efficacy of SSRI treatment is the result of action on the nuclear aspects of the disease, or action on other clinical and psychopathological elements that characterize the disturbance (e.g. depressive mood, impulsivity, obsessive thinking) (10, 11). The use of SSRIs in anorexia nervosa is also limited by problems relating to tolerability and to patient compliance (9).

Recently citalopram, one of the highly selective SSRIs, has proved to be effective in depression (12, 13), and its efficacy has also been documented in Obsessive Compulsive Disorder (OCD) (14, 15). The pharmacokinetic profile of citalopram is characterized by a low potential for causing clinically important interactions with CYP2D6 substrates. Its tolerability profile is superior to that of tricyclic antidepressants and recent studies have demonstrated its more favourable profile compared to other SSRIs (16). A specific effect on appetite increase has also been recently suggested (17). For these two reasons, citalopram seems a particularly interesting possibility for the treatment of eating disorders, particularly anorexia nervosa, because of its possible specificity of action and its tolerability in subjects who are often prostrated.

The aim of the present study is to evaluate the efficacy of citalopram in a group of anorectic restricting patients.

METHOD

There was a 6-month, open medication trial of citalopram in the treatment of outpatients with anorexia nervosa, restricting subtype, who had been diagnosed according to DSM IV criteria.

Patients were interviewed following the Structured Clinical Interview for Axis-I DSM IV disorders (SCID-I) (18) schedule for diag-

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nosis. From the initial group, 3 patients were not enrolled because of the presence of a clinical depressive state (assessed through the clinical interview), and they were excluded from further analysis. This was in order to assess the effect of citalopram independently from its antidepressant action.

The subjects who entered the trial were 32 anorectic outpatients, all females, aged 17-33 (m=22.3, s.d.: 4.0), the mean length of illness was 6.4 yrs., s.d. 3.7, and educational level was 10.9 yrs, s.d. 3.6. Patients started on the citalopram trial during refeeding and weight restoration (range 72-84% Ideal Body Weight [%IBW]; mean 77.7%, s.d. 3.7). All the patients were amenorrhoic at enrollment. Prior to the citalopram trial, patients underwent a 2-week evaluation period during which patients received no psychotropic medication. The criteria for exclusion from the study included a history of psychotic symptoms or focal neurological disorders, systemic illness, prior treatment with electroconvulsive therapy, substance dependence or drug abuse. Patients were considered to have dropped out when citalopram was taken for less than 6 months from the time of enrollment.

The starting dose was 20 mg of citalopram. No concurrent treatments were administered during the citalopram treatment period. Patients who showed clinical improvement after 4 weeks were maintained on 20 mg of citalopram. In patients who did not minimally improve (as reported at weekly clinical evaluations) and did not report severe side effects, citalopram was titrated to 30 mg after 4 weeks, to 40 mg after 6 weeks, to 50 mg after 8 weeks and to 60 mg after 10 weeks.

Moreover, each patient received a nutritional programme at the beginning of the trial which consisted in suggesting a gradual increase in calorie intake from 1000 to 2500Kal/day, together with weekly weight checks.

Medication was administered following the guidelines of the Fluoxetine Clinical Use Manual (19).

The staff saw each subject at regular intervals. The frequency of appointments ranged from once per week to once per 4 weeks, and clinical evaluations and adverse effect assessment (open-ended) were recorded during each visit. The Eating Disorder Inventory ED1-2 (20) was administered to assess current eating behavior, the Symptoms Checklist-90-Revised (SCL-90R) (21) was used to measure general psychopathology, depressive symptoms were measured using the Hamilton Rating Scale for Depression (Ham-D) (22) and obsessive and compulsive symptoms with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (23, 24).

Response was determined by the following criteria:

Satisfactory response: at least two of the following: 1) weight increase >= 5% from enrollment; 2) menstruation; 3) SCL 90-R improvement = 35%.

Unsatisfactory response: none or only one of the criteria for satisfactory response.

A complete description of the study was given to the subjects and written consent was obtained before a patient entered the study trial. For the Intention-to-treat protocol, patients who dropped out after concluding the 6-month citalopram trial were also included in the analysis, the data being based on evaluations at the drop-out point.

STATISTICAL PROCEDURES

Statistical analyses were carried out using the SPSS-PC statistical package. Between-group comparisons were made using one-way ANOVA, assessing the significance of differences between the groups with alpha set at $p<0.05$, two tailed.

RESULTS

Table 1 presents the % Ideal Body Weight (%IBW) variations from the baseline in anorectics treated with citalopram, together with the SCL-90R score change and demographic data. Six (18.7%) patients discontinued the treatment before completing the 6-month trial, while twenty-six (81.2%) patients concluded the trial. The entire group of anorectics (n=32) showed a significant difference between the mean %IBW at the beginning and at the end of the study [enrollment m: 77.7, s.d. 3.7; end of trial m: 81.3, s.d. 5.7; F=8.98, degrees of freedom (d.f.) 63, p<.01]. The mean Ham-D score of anorectics at enrollment was 10.3 (s.d. 3.7); the mean Y-BOCS score at enrollment was 8.7 (s.d. 3.9).

At the end of the trial we found no significant differences in Ham-D scores (m: 8.6, s.d.: 4.5; F=2.7; n.s.) and Y-BOCS (m: 6.9,

TABLE 1
Demographic and clinical data of 32 female anorectic patients.

Patient	Response Onset	Age at Onset	Age at Treatment	Ham-D	Low %IBW	Months On Citalopram	Maximum Dose (mg/d)	%IBW Start	%IBW End	Weight Change	menstruation	SCL 90-R Improvement %
1	Satisfactory	12	19	15	61	6	40	78	83	5	No	38%
2	Satisfactory	15	20	15	80	6	40	81	91	10	Yes	30%
3	Satisfactory	20	33	10	63	6	40	79	86	7	No	46%
4	Satisfactory	13	24	15	59	6	30	75	80	5	No	66%
5	Satisfactory	15	18	13	77	6	20	80	88	8	No	39%
6	Satisfactory	17	26	13	65	6	40	74	83	9	No	58%
7	Satisfactory	11	19	6	67	6	20	79	85	6	No	47%
8	Satisfactory	19	21	9	78	6	20	83	90	7	Yes	52%
9	Satisfactory	16	24	14	62	6	40	82	87	5	No	40%
10	Satisfactory	15	20	6	69	6	40	77	85	8	No	68%
11	Satisfactory	13	19	8	79	6	40	84	89	5	No	33%
12	Satisfactory	12	18	12	77	6	40	82	90	8	Yes	58%
13	Satisfactory	12	17	6	68	6	60	79	86	7	No	35%
14	Satisfactory	18	24	5	77	6	20	81	85	4	Yes	46%
15	Satisfactory	21	26	6	76	6	30	83	87	4	Yes	52%
16	Unsatisfactory	19	32	15	58	6	40	76	79	3	No	40%
17	Unsatisfactory	20	23	11	61	6	40	72	77	5	No	30%
18	Unsatisfactory	16	19	9	69	6	60	76	76	0	No	27%
19	Unsatisfactory	14	19	11	68	6	20	75	78	3	No	10%
20	Unsatisfactory	17	21	10	73	6	60	80	81	1	No	-15%
21	Unsatisfactory	13	20	11	75	6	40	76	76	0	No	42%
22	Unsatisfactory	15	23	4	58	6	40	74	77	3	No	-6%
23	Unsatisfactory	18	28	13	80	6	60	82	81	-1	No	37%
24	Unsatisfactory	17	18	10	75	6	40	78	75	-3	No	7%
25	Unsatisfactory	16	24	9	67	6	60	79	75	-4	No	21%
26	Unsatisfactory	11	19	16	64	6	60	73	79	6	No	11%
27	Dropped out	17	20	15	69	2,5	20	81	81	0	No	9%
28	Dropped out	20	24	6	74	1,5	20	77	79	2	No	-21%
29	Dropped out	16	26	4	71	1	20	72	70	-2	No	-13%
30	Dropped out	19	21	14	70	1	10	73	73	0	No	-6%
31	Dropped out	13	22	9	63	2,5	20	73	74	1	No	10%
32	Dropped out	21	27	8	71	4,5	40	72	75	3	No	16%
Satisfactory	Mean	15,3	21,9	10,2	70,5	6,0	34,7	79,8	86,3	6,5	Yes: 33,3%	47,2
	SD	3,2	4,3	3,8	7,5	0,0	11,3	2,9	3,0	1,8	No: 66,7%	11,7
Unsatisfactory	Mean	16,0	22,4	10,8	68,0	6,0	47,3	76,5	77,6	1,2	Yes: 0%	18,5
	SD	2,6	4,3	3,2	7,3	0,0	13,5	3,0	2,2	3,2	No: 100%	18,8
Dropped out	Mean	17,7	23,3	9,3	69,7	2,2	21,7	74,7	75,3	0,7	Yes: 0%	-0,8
	SD	2,9	2,8	4,4	3,7	1,3	9,8	3,6	4,0	1,8	No: 100%	14,7
Total	Mean	16,0	22,3	10,3	69,5	5,3	36,6	77,7	81,3	3,6	Yes: 15,6%	28,3
	SD	3,0	4,0	3,7	6,8	1,6	14,7	3,7	5,7	3,6	No: 84,4%	24,1

Ham-D: Hamilton rating scale for Depression. %IBW: %Ideal Body Weight. SCL 90 R: Symptom Checklist 90R.

s.d.: 4.2; F=3.2; n.s.) compared with the beginning. According to the response criteria, of the 32 enrolled anorectic patients, 15 (46.9%) showed a satisfactory response at the end ofthe trial, with a mean gain of 6.5% IBW (s.d.: 1.8) and a SCL-90R improvement score percentage of 47.2% (s.d.: 11.7). Five anorectic patients with a satisfactory response had regained menstrual cycles by the end of the trial. Eleven patients (34.4%) demonstrated an unsatisfactory response to citalopram, with a SCL-90R improvement score percentage of 18.5% (s.d.: 18.8) and no cases of menstrual recovery. The maximal citalopram dose was lower in the satisfactory response group (m: 34.7 mg., s.d.: 11.3) and higher in the unsatisfactory response group (m: 47.3 mg., s.d.: 13.5), and this difference was significant (F: 6.7; d.f.: 25; p<.05). No significant differences were found among these two outcome-based subgroups in age at onset (F=.24; n.s.), age at treatment (F=.09; n.s.), lowest %IBW (F=.72; n.s.), while patients with unsatisfactory response to citalopram had a significantly lower %IBW at the beginning of treatment (F=7.98; p<.01). No differences were found between the two subgroups on the Ham-D score (F=.2; n.s.) and SCL-90R severity at enrollment (F: 2.34; n.s.). The subgroup of patients who dropped out (n=6) showed a significantly lower %IBW at the beginning of the treatment compared to all the patients who ended the 6-month trial (m: 74.7, s.d.: 3.6; vs. m: 78.4, s.d.: 3.4; F: 5.7, d.f.: 31, P<.05). Specifically, patients who dropped out showed a significantly lower %IBW at the beginning compared with the satisfactory response subgroup (F: 11.6; d.f.: 20; p<.01), and no significant %IBW differences compared to the unsatisfactory response subgroup (F: 1.2; d.f.: 16; n.s.).

The whole group of anorectics showed a significant reduction of severity scores in several EDI-2 scales after 6 months of treatment with citalopram, compared with the same group at the beginning of the treatment (Table 2). In particular, the subscales where we found the highest score improvement were: drive for thinness (F=11.3; p<.01), ineffectiveness (F=10.1; p<.01), impulse regulation (F=10.3; p<.01), and social insecurity (F=7.4; p<.01). A lesser difference, although significant, was in the perfection (F=4.3; p<.05) and interpersonal distrust subscale (F=5.; p<.05), and no significant differences were found in the other EDI-2 subscales. At the end of the trial, patients who had a good response with citalopram also revealed a significantly greater amelioration of their clinical psychopathological state, as measured by the SCL-90R GSI, compared to the partial and poor response groups (F=4.17; p<.05).

The adverse effects which emerged during the treatment were principally those of a dry mouth (25% of the patients), somnolence (25%), asthenia (21.8%), nervousness (18.7%), nausea (12.5%), constipation (12.5%), increased sweating (9.4%), tachycardia (6.2%), tremor (6.2%).

TABLE 2

EDI-2 subscale scores (0-30) in the group of anorectic patients at the beginning and at the end of the trial (n=32). For the Intent-to-treat protocol, the patients who dropped out were also included, evaluated at the drop-out point

EDI-2 subscales	TRIAL BEGINNING	TRIAL END	ANOVA f
Drive for thinness	17.6 (4.9)	13.8 (4.1)	11.3**
Bulimia	3.9 (3.1)	2.6 (2.8)	3.1
Body dissatisfaction	14.6 (4.7)	13.5 (4.1)	1.0
Ineffectiveness	12.1(4.4)	8.8 (3.9)	10.1**
Perfection	7.0 (3.8)	5.2 (3.1)	4.3*
Interpersonal distrust	8.9 (4.5)	6.3 (4.3)	5.6*
Interoceptive awareness	9.0 (4.7)	6.9 (3.9)	2.6
Maturity fears	8.4 (3.6)	7.4 (3.8)	1.2
Ascetism	8.6 (3.2)	7.8 (3.5)	0.9
Impulse regulation	10.9 (4.7)	7.4 (4.0)	10.3**
Social insecurity	10.1(4.8)	6.9 (4.6)	7.4*

1-way Anova (d.f.=63): *p<.05 **p<.01.

CONCLUSIONS

At the end of the trial, 15 of the 32 patients (46.9%) showed a satisfactory response, with a drop-out rate of 18.7%. The open administration of citalopram seems to be very encouraging.

These findings are particularly important because they were carried out on a sample of anorexic patients who were exclusively of the restricting subtype, without comorbidity in terms of depressive disorder. In contrast, the two previous trials with fluoxetine (9, 10) were conducted on an anorexic population

including patients with restricting eating behavior or anorexics who binged and/or purged, with comorbidity of depression and obsessive disorders. In the study of fluoxetine (10), drug administration was associated with weight gain in relation to a reduction in depression and a decrease of obsessive thoughts about food and ritualistic preoccupations. In our sample, amongst the improvement criteria we established not only the Ideal Body Weight percentage (%IBW), but also menstruation recovery and SCL-90R evaluation. As this was a study conducted on patients on an out-patient basis with a subsequent check-up, the weight improvement can be considered reassuring. It will, however, be necessary to continue the follow-up process for 12 months.

In addition, in our sample the drop-out rate is particularly low and despite the increase of the dosages in the non-responsive cases, there were no cases of binge-eating or of mood switch which further confirms its specific tolerability. Satisfactory response correlates with a dose that is lower on average and so does not seem to depend on the dose but on a specific sensitivity to treatment.

Several EDI-2 subscales showed a statistically-significant decrease following citalopram treatment: drive for thinness, ineffectiveness, impulse regulation, social insecurity, perfection, interpersonal distrust. The good response subgroup in particular showing a higher improvement. These results coincide with an improvement of their psychopathological state at the end of the trial, whereas in some literature (25), EDI bulimia, ineffectiveness, perfectionism and interpersonal distress subscale scores have correlated significantly with severity of depression. Of the EDI subscales that have not had a significant decrease, Body Dissatisfaction (BD) is one of those with a smaller decrease after pharmacological therapy. In the current literature there are no data relative to the effect of drugs on the BD subscale of EDI in anorexia, while there are data on the decrease of the values of this subscale with pharmacotherapy and psychotherapy in cases of bulimia (1, 26, 27). It remains to be established if BD is an item that can be functionally referred to a thought disorder linked to body perception. In this respect, not even the data relative to the use of neuroleptics have had positive confirmation or those referring to a mode of interacting with the environment. It should be stressed that the SSRIs have also demonstrated their efficacy in relation to other pathologies, the basis of which are constituted by alterations of body perception and of the control of impulses. This emerges in particular from studies on Body Dysmorphic Disorder (28-30) and other studies conducted on impulse-discontrol disorders: kleptomania (31), tricotillomania (32), gambling (33), Auto-mutilating Disorder (34).

If further research confirms these results, citalopram will be a candidate for becoming a useful agent in the treatment of anorexia nervosa.

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Efficacy of citalopram in anorexia nervosa: a pilot study

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Abstract

Introduction: Anorexia nervosa (AN) still lacks a defined treatment. Since fluoxetine proved effective in weight-restored anorexics, this pilot study evaluates the efficacy of another SSRI, citalopram, in restricting-type AN. *Experimental procedures:* Fifty-two female anorectic outpatients were randomized in the citalopram (n=26) and waiting list (n=26) as a control group. Efficacy was assessed using Eating Disorder Inventory-2, Eating Disorder Inventory-Symptom Checklist, State-Trait Anger Expression Inventory, Beck Depression Inventory, Symptom Checklist-90 and Structured Clinical Interview for DSM-IV Axis II Disorders. *Results:* Thirteen patients dropped-out, thus 19 patients received citalopram and 20 remained in the control group. After 3 months of treatment, the citalopram group showed a decrease on BDI and SCL-90 Depression subscale and an improvement of baseline obsessive compulsive features on SCL-90, EDI-2 impulsiveness and Trait-anger on STAXI. Weight gain was similar in the two groups. *Discussion:* These preliminary results support the efficacy of citalopram in anorectics. Citalopram seems to improve depression, obsessive–compulsive symptoms, impulsiveness and Trait-anger.

Keywords: Anorexia nervosa; Selective serotonin reuptake inhibitors; Citalopram

1. Introduction

Anorexia nervosa (AN) is a complex disorder that occurs predominantly in young women (American Psychiatric Association, 1994). It is believed to be determined by many factors but its etiology is uncertain. As a consequence there is still no proven or unequivocal treatment for this disorder (Ferguson et al., 1999; Herzog et al., 1992). According to some authors (Jimerson et al., 1996) adjunctive pharmacotherapy in the treatment of hospitalized patients has few benefits. Other authors have reported as useful clomipramine (Crisp et al., 1987), cyproheptadine hydrochloride (Halmi et al., 1986; Goldberg et al., 1979; Vigersky and Loriaux, 1977) and monoamine oxidase inhibitors (Johnson et al., 1983; Hudson et al., 1985).

Recently, numerous studies using selective serotonin reuptake inhibitors (SSRIs) have been conducted, but the results are inconsistent. Strober et al. (1997) demonstrated that fluoxetine, in addition to other therapies, did not significantly improve outcome. An open-trial study has, however, demonstrated the effectiveness of fluoxetine on weight, obsessive thoughts, and depression (Gwirtsman et al., 1990). Further studies to explain these different results suggested that the effectiveness of fluoxetine depends on the clinical condition of the patient. Kaye and co-workers found that in weight-restored AN patients fluoxetine improved outcome and reduced relapse (Kaye et al., 1991; Kaye, 1997). Attia et al. (1998) demonstrated the ineffectiveness of fluoxetine in underweight patients. A retrospective study further demonstrated that all SSRIs are ineffective in malnourished underweight patients with AN (Ferguson et al., 1999). This hypothesis is also supported in a review by Kaye et al. (1999). It is as yet unclear whether fluoxetine or other SSRIs can be used before complete weight restoration as it is difficult to derive consistent responses from the above-mentioned studies.

Until recently only a few reports in the literature have

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discussed the use of other SSRIs in the treatment of AN (Calandra et al., 1999; Raitasuo et al., 1998; Bergh et al., 1996). Further explorations are justified because these compounds are known to influence the depressive and obsessive aspects of AN, which are extremely important from clinical and genetic viewpoints (Lilenfeld et al., 1997; Casper, 1990; Kaye et al., 1998; Collier et al., 1997; Enoch et al., 1998). Besides, as demonstrated by studies on the cerebrospinal fluid 5-hydroxyindoleacetic acid (5-HIAA) factor (Kaye et al., 1998) and on the temperamental trait Harm Avoidance (Cloninger et al., 1993; Fassino et al., in press), some pathological behaviors common in AN could be linked to serotonergic activity.

Citalopram is the most recent SSRI. It is characterised by a more selective pharmacological profile with respect to other compounds of this class, and it is safe (Bezchlibnyk-Butler et al., 2000; Tan and Levin, 1999; Feighner and Overo, 1999).

The aim of this pilot study was to examine the efficacy of citalopram in the treatment of outpatients suffering from restricting-type AN. Primary outcome measures were eating symptoms and psychopathological symptoms were considered. Moreover, one objective was to verify whether changes noted after pharmacological treatment are independent from possibly confounding variables such as age, years of disease, body mass index (BMI), and personality disorders.

2. Experimental procedures

2.1. Study design

A prospective, randomized, controlled study of the efficacy of citalopram in outpatients with restricting-type AN. The control group comprised restricting-type AN outpatients receiving no drug treatment (waiting list). The study was conducted in accordance with the Helsinki declaration. Written informed consent was obtained from all patients prior to enrolment.

2.2. Patient selection and procedures

Subjects were recruited from the anorectic outpatient population of the Centre for Eating Disorders, Turin University from 1 September 1998 to 1 September 2000. The inclusion criteria were: diagnosis of restricting-type AN, age 16–35 years and not being under psychopharmacological therapy during the month preceding the beginning of the study (6 weeks if the drug was fluoxetine) or estrogen–progesterone therapy. The exclusion criteria were a psychiatric comorbidity and known sensitivity to citalopram.

All patients meeting the inclusion criteria were enrolled into the study after diagnostic assessment. All eligible patients were included on a waiting list to receive an integrated treatment (dietary and psychiatric treatment), which represents the usual practice at the Centre for Eating Disorders (Fassino et al., 1998). Using a random allocation, the patients were divided in two groups: treatment group (citalopram therapy) and control group (waiting list without drug therapy).

Dosage and possible side effects of treatment were explained to the patients in the citalopram group. The study treatment was provided free of charge. Citalopram was administered after the evening meal, starting at 10 mg/day and increased to 20 mg/day after 6 days of therapy for at least 12 weeks. The patients in the control group did not receive citalopram but were followed by a periodic clinical assessment and test administration, in the same way as for the citalopram group. The only other psychoactive treatment allowed (in four patients) was lorazepam (up to 4 mg/day), if needed for control of anxiety, agitation, or insomnia.

2.3. Study assessments

Two psychometric tests were used for the evaluation of Eating Disorder (ED) and four instruments for the evaluation of psychopathological traits. Eating Disorder evaluation involved the Eating Disorder Inventory-2 (EDI-2) to investigate the psychological traits typical of this disorder (Drive for Thinness, Bulimia, Body Dissatisfaction, Ineffectiveness, Perfectionism, Interpersonal Distrust, Interceptive Awareness, Maturity Fears, Asceticism, Impulse Regulation, Social Insecurity) and the Eating Disorder Inventory-Symptom Checklist (EDI-SC) to evaluate frequency and features of the basic behaviors of ED (Garner, 1991).

Psychopathological traits were assessed using the State-Trait Anger Expression Inventory (STAXI) for the assessment of the experience and expression of anger (Spielberger, 1983); the Beck Depression Inventory, simplified version of 13 items (BDI) (Beck, 1978); the Hopkins Symptom Checklist (SCL-90) (Derogatis, 1977), and the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) (First et al., 1995). During the first assessment (T0) all patients were interviewed to collect medical, psychiatric, and pharmacological history.

In all patients body weight, eating behavior, and psychopathological symptoms were evaluated at baseline and on days 14, 28, 41, 46, 70, and 84. In the patients in the citalopram group, possible side effects were also evaluated. EDI-2, EDI-SC, BDI, and STAXI were administered at baseline and on days 28, 56, and 84. SCID-2 was administered at baseline and completed with the interview on day 4 or 5. The SCL-90 was administered at baseline and on day 84.

2.4. Statistical analysis

To evaluate the benefit of citalopram on the treatment of AN, only measures observed at baseline and at time T3

have been considered in the analysis. Approximation to the normal distribution of the study variables was not possible; for this reason, nonparametric methods have been used in the analysis. A multivariate analysis was performed to evaluate the efficacy of citalopram treatment on the differences mentioned, considering confounding factors.

A univariate analysis (Wilcoxon test for paired data) have been performed comparing variations of parameters in study between baseline level and time T3 separately in the two groups. When a significant variation, or no variation, between time T0 and time T3 was found in both groups, no difference between treatments was assumed.

Then a multivariate analysis has been performed: a multiple regression model, where the effect of citalopram treatment (independent variable) on each of the outcome variables was adjusted for the principal confounding factors.

In the first model BMI has been considered the outcome variable and age, years of disease, SCID II score as adjusting variables. In the second model differences between measures (T3–T0) for each clinical test item have been considered the outcome variables and age, years of disease, SCID II score, BMI at baseline as adjusting variables.

All analyses were performed using SPSS 8.0 (SPSS, Chicago, IL, 1998).

3. Results

3.1. Study sample

The first 98 consecutively admitted anorectic patients were considered for inclusion. Fifty-two patients with restricting-type AN were eligible and randomly assigned to the citalopram (n=26) or control group (n=26). Seven patients in the citalopram group (29.6%) and six patients in the control group (30%) did not complete the study, leaving 19 and 20 patients in the two groups, respectively. Patients who dropped out of the study did not differ significantly from those who completed it in terms of age, age of onset, duration of illness, and duration of amenorrhea.

Baseline demographic and clinical characteristics were comparable in both groups. Age, age of onset, duration of illness, and duration of amenorrhea were similar in the two groups (Table 1).

3.2. Univariate analysis

A significant increase in weight and BMI emerged from the analysis in both groups (Table 2 and Fig. 1). However, there was a significant decrease in the BDI score, which evaluated depressive symptoms, only in the citalopram group (Table 2). Similarly, in the citalopram group there was a significant improvement in anger and in some psychopathological dimensions measured by EDI-2 and SCL-90, as summarized in Table 3.

Table 1
Age of patients, onset, years of disease, and duration of amenorrhea

	Citalopram group	Control group	P value
Age:			
Mean	24.346	25.230	0.819
S.D.	5.381	8.645	
Age of onset:			
Mean	18.423	17.692	0.549
S.D.	4.159	3.916	
Duration of disease (years):			
Mean	5.692	7.538	0.811
S.D.	4.905	8.188	
Duration of amenorrhea (months):			
Mean	15.807	20.115	0.898
S.D.	14.827	25.346	

S.D., standard deviation.

3.3. Multivariate analysis

As shown in Table 4, only some of the previous variations between T0 and T3 retained their significance after controlling for confounding variables (age, duration of disease, personality disorders, BMI at baseline). Improvement in depressive symptoms as well trait anger improvement maintained significance. For the EDI-2 scales, improvements in ineffectiveness and impulsiveness remained significant. For the SCL-90 scales, improvements in depression, obsessive–compulsive, and somatization were significant.

4. Discussion

The results can be discussed on three different levels. First, on the basis of previous literature improvements in depression and obsessiveness were expected. Second, some of the results obtained (anger and impulsiveness, somatization) were unexpected but are significant with respect to the effectiveness of SSRIs in AN. Finally, weight improvement is also discussed as a discriminating parameter for the effectiveness of SSRIs in AN patients. Only the results which were independent of confounding factors are discussed, also because the methodological weakness of having not a placebo controlled group diminishes the confidence of the results.

4.1. Depressive symptoms

The BDI score in the total sample (13.55 at baseline) confirms the important role that depressive symptoms play in AN. It does not, however, satisfy the DSM-IV criteria for the diagnosis of Mood Disorders (as requested in the

Table 2
Variations (baseline to 3 month) in weight, BMI, and Beck Depression Inventory index

	Citalopram group				Control group			
	T0	T3	Difference (T3–T0)	*P* value	T0	T3	Difference (T3–T0)	*P* value
Weight:								
Mean	43.48	46.47	2.99	0.003	42.48	43.92	1.44	0.007
S.D.	3.93	5.33			4.60	4.86		
BMI:								
Mean	16.19	17.47	1.28	0.002	15.62	16.33	0.71	0.005
S.D.	0.81	1.41			1.42	1.68		
BDI:								
Mean	14.46	7.31	−7.15	0.001	12.65	12.30	−0.35	0.943
S.D.	7.73	5.07			6.39	9.02		

S.D., standard deviation; BDI, Beck Depression Inventory.

inclusion criteria). As was expected, depressive symptoms improved after 3 months of treatment with citalopram. This was confirmed by the significant reduction in BDI score, in SCL-90 item 'Depression' and in EDI-2 scale 'Ineffectiveness'. Calandra et al. (1999) obtained similar results in bulimic patients.

4.2. Obsessive–compulsive traits

Because SSRIs are indicated for Obsessive–Compulsive Disorder, an improvement in scores correlated to these disorders was expected to be found. Previous studies have also demonstrated the effectiveness of fluoxetine in obsessive symptoms associated with ED (Gwirtsman et al., 1990; Kaye et al., 1991; Kaye, 1997). As expected, the obsessive–compulsive features measured with the SCL-90 and Impulse Regulation measured with the EDI-2 significantly improved.

4.3. Anger and impulsiveness

Many authors have suggested that bulimic behaviors in AN and Bulimia Nervosa are due to the presence of a multi-impulsive disorder (Kaye et al., 1998; Lacey, 1993;

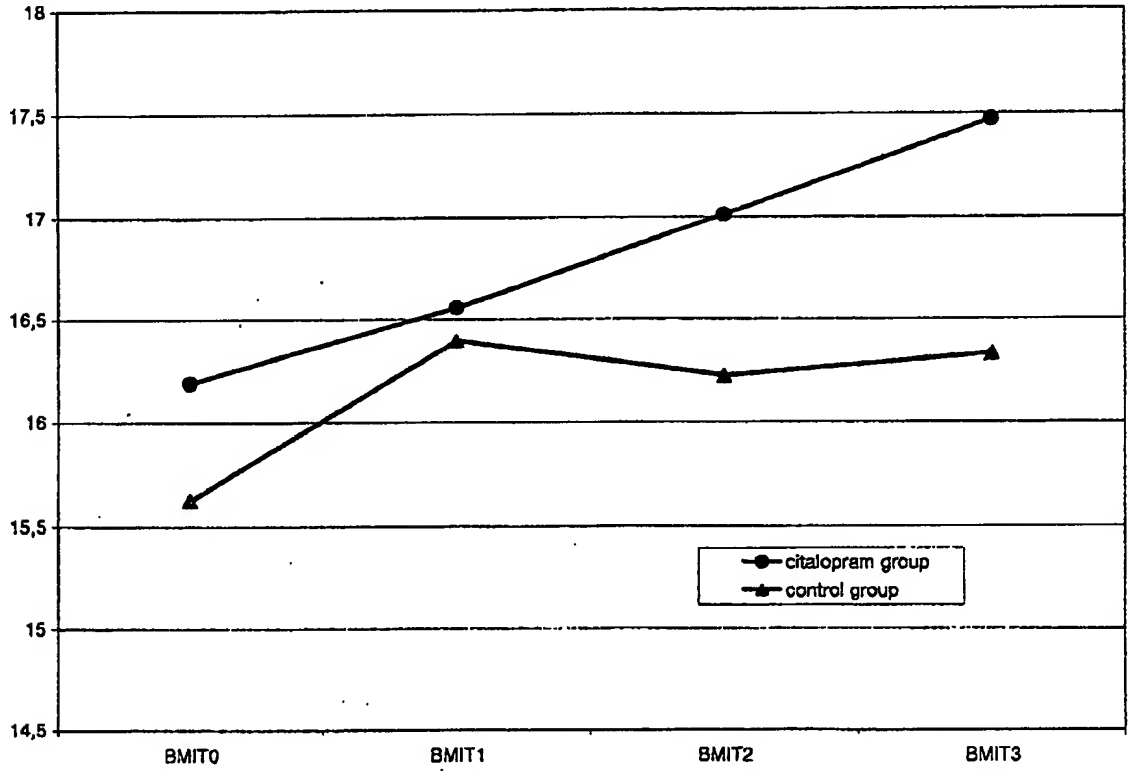

Fig. 1. Mean BMI: change from baseline in treatment and control group.

Table 3
Mean scores of some STAXI, EDI-2, and SCL-90 items (baseline and 3 month) in both groups

Test	Scale	Citalopram group				Control group			
		T0	T3	Difference (T3–T0)	*P* value	T0	T3	Difference (T3–T0)	*P* value
STAXI	*Temperamental anger*								
	Mean	21.23	17.58	3.65	0.011	20.50	19.90	0.60	0.899
	S.D.	5.41	4.23			5.29	6.52		
	Anger reaction								
	Mean	9.61	8.31	1.30	0.049	9.27	9.25	0.02	0.514
	S.D.	2.14	2.31			2.96	3.49		
EDI-2	*Bulimia*								
	Mean	5.88	2.26	3.62	0.005	3.31	3.30	0.01	0.614
	S.D.	6.71	4.07			3.66	3.67		
	Ineffectiveness								
	Mean	12.35	5.63	6.72	0.002	8.23	8.05	0.18	0.651
	S.D.	8.79	3.85			6.55	7.24		
	Interpersonal distrust								
	Mean	7.11	4.47	2.64	0.014	5.07	4.00	1.07	0.909
	S.D.	4.59	3.76			4.20	4.04		
	Impulse regulation								
	Mean	7.50	2.74	4.76	0.001	6.69	5.80	0.89	0.270
	S.D.	5.41	3.41			6.01	5.18		
SCL-90	*Somatization*								
	Mean	17.84	13.95	3.89	0.005	14.65	13.45	1.20	0.806
	S.D.	10.25	7.11			8.17	5.66		
	Obsessive–compulsive								
	Mean	18.08	13.79	4.29	0.002	14.11	14.05	0.06	0.572
	S.D.	8.54	7.72			8.85	8.47		
	Depression								
	Mean	26.73	17.11	9.62	0.001	23.69	22.55	1.14	0.489
	S.D.	11.56	9.39			12.49	12.78		
	Anxiety								
	Mean	17.38	12.74	4.64	0.005	15.65	14.15	1.50	0.054
	S.D.	8.16	6.59			9.26	8.78		
	Paranoid ideation								
	Mean	10.04	7.79	2.25	0.004	8.27	7.15	1.12	0.083
	S.D.	5.33	3.78			6.56	5.68		
	Psychoticism:								
	Mean	11.15	7.68	3.47	0.017	7.92	6.80	1.12	0.196
	S.D.	6.69	4.63			5.95	5.84		

S.D., standard deviation; STAXI, State-Trait Anger Expression Inventory; EDI-2, Eating Disorder Inventory-2; SCL-90, Symptom Checklist-90.

Nagata et al., 2000). Boris (1984) suggests that in AN the impulsiveness is at the core of obstinate refusal of food and of the defensive attitude. Anger also plays a major role in the pathogenesis and the maintenance of AN symptoms (Keen, 1996; Fassino et al., 2001a,b).

These dimensions have received little attention in previous studies on the use of SSRIs in AN (Ferguson et al., 1999; Strober et al., 1997; Kaye et al., 1991; Attia et al., 1998). It is, therefore, important to consider the effectiveness of citalopram on anger and impulsiveness in the first 3 months of treatment. Temperamental or Trait anger measured by STAXI, which evaluates disposition toward anger, improved significantly after 3 months of treatment with citalopram, independently from confounding factors. In addition, Impulsiveness improved significantly following citalopram treatment, as shown by the reduction of the score of the Impulse Regulation scale in EDI-2. These improvements could also be associated with each other from a clinical viewpoint (Fassino et al., submitted).

4.4. Somatization

The improvement of Somatization is statistically significant, and this change could facilitate patients' ability to

Table 4
Importance of treatment on BDI, STAXI, EDI-2, and SCL-90 (standardised coefficient β) crude and adjusted by confounding factors (age, age of onset, duration of disease and basal BMI)

Test	Crude β	Adjusted β
BDI	0.42**	0.41**
STAXI:		
Temperamental anger	0.34*	0.35*
Reaction of anger	0.21	0.31
EDI-2:		
Bulimia	0.35*	0.29
Ineffectiveness	0.49**	0.45**
Interpersonal distrust	0.34*	0.31
Impulse regulation	0.52**	0.54**
SCL-90:		
Somatization	0.33*	0.35*
Obsessive–compulsive	0.47**	0.46**
Depression	0.43**	0.42*
Paranoid ideation	0.28	0.29

*$P<0.05$; **$P<0.01$.

face problems more directly as well as to help eliminate maladaptive behaviors, such as somatization.

4.5. Weight and BMI

During this study, body weight and BMI significantly increased both in the citalopram and control groups (Fig. 1). The starting mean BMI values were 16.19 and 15.62, respectively. There were no significant differences in the weight gain in the two groups. Weight gain did not, therefore, seem to be a specific effect of citalopram, as also reported for fluoxetine in previous studies (Ferguson et al., 1999; Kaye et al., 1991).

Weight gain may be due to a positive effect of clinical care of the patients during the 3-month study period.

5. Conclusions

The use of citalopram in restricting-type AN outpatients demonstrated promising results, also because these improvements were not influenced by important factors such as duration of the disease, age, weight, or presence of personality disorders. Furthermore these results also provide insight into some psychopathological traits that have not received much consideration to date. On the other hand there are three main limitations to our study. First, the effect on depression complicates the analysis because it is not clear whether some of the clinical improvements are secondary to an effect of citalopram on depression. Second, our study was not designed for very low weight anorectic patients, because it was conducted in an outpatient department. Even though we have found no differences in the outcome improvement between patients with higher BMI and patients with a lower one, the absence of severely underweight anorectics in our sample does not allow to generalize our results. For example subjects with a mean BMI over 16 could respond to antidepressant medication in a different way from the very low weight anorexics (Ferguson et al., 1999; Kaye et al., 1991; Attia et al., 1998; Kaye et al., 1998). Last, a methodological weakness of this study is that its design was not double-blind, placebo-controlled. Such a design would have decreased the halo effect. In the present study the researcher might have a tendency to overestimate the improvements obtained in the citalopram group in anger and impulsiveness, owing to the improvement of both depressive and obsessive symptomatology due to the assumption of the drug. Of course, the halo effect decreases the confidence in the results, though the perceivers' overestimation of the results obtained might have been partly reduced by the use of self-administered questionnaires.

Notwithstanding this methodological bias we believe that some interesting considerations on the use of citalopram in anorexia nervosa emerge from the present study, especially considering that up to now in literature there are not yet specific studies on this subjects, not even with an open design. The use of a no treatment control group in the present study, with respect to an open trial, allows at least the distinction of the drug effect from some non-specific factors which might contribute to healing, first of all, the natural illness course. Moreover, as regards the control group, subjects were visited as outpatients and administered questionnaires in the same way of the citalopram group; this might have elicited a placebo response or 'response to the healing situation' as a consequence of the symbolic impact of treatment setting (Papakostas and Daras, 2001). This placebo effect might in part balance the placebo effect which has certainly contributed to the improvement of patients in the citalopram group, thus increasing the possibility to compare of the two groups.

In conclusion, stronger evidence will be available with randomized, placebo controlled trials, evaluating the efficacy of citalopram in a larger and more comprehensive sample. Such trials are in fact still the best way to perform a clinical trial sustaining the efficacy of a drug (Montgomery, 1999). If the preliminary results of this pilot study will be confirmed citalopram may be particularly beneficial in the therapy of AN for its benefits on depression and obsessive–compulsive symptoms and its action on some aspects of the pathogenic core of this disease, such as anger and impulsiveness.

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